FINAL STATEMENT OF REASONS
22 CALIFORNIA CODE OF REGULATIONS

SECTIONS 12705(b) and 12705(d). SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

This is the Final Statement of Reasons for specific regulatory levels posing no significant risk for eight chemicals listed as known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (hereinafter "the Act" or Proposition 65; Health and Safety Code 25249.5 *et seq*.). On June 13, 2003, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt regulatory levels for ten chemicals listed pursuant to the Act as known to the State to cause cancer (Title 22 Cal. Code of Regs. §12000) (benz[a]anthracene, benzene, benzo[b]fluoranthene, benzo[j]fluoranthene, bromoform, chrysene, 7H-dibenzo[c,g]carbazole, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, and 5-methylchrysene). The Notice also announced a proposed regulatory level for adoption in Title 22 Cal. Code of Regs. §12805 for one chemical listed as known to cause reproductive toxicity (Title 22 Cal. Code of Regs. §12000) (arsenic [inorganic oxides]). The Initial Statement of Reasons set forth the grounds for the proposed regulations.

Pursuant to the Notice of Proposed Rulemaking, a public comment period was held between June 13 and July 31, 2003, and a public hearing was held on July 31, 2003.

Final regulations for two chemicals included in the original Notice of Proposed Rulemaking, benzene and bromoform, were adopted on May 12, 2004. A regulation for arsenic (inorganic oxides) will be proposed at a later time. This regulation hereby adopts regulatory levels for eight chemicals, all in the class of chemicals termed polycyclic aromatic hydrocarbons, included in the original Notice of Proposed Rulemaking: benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, 7H-dibenzo-[c,g]carbazole, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, and 5-methylchrysene.

UPDATE OF INITIAL STATEMENT OF REASONS

UPDATE OF TECHNICAL INFORMATION IN THE INITIAL STATEMENT OF REASONS

All data, studies, reports, or other documents relied on for this regulation were identified in the Initial Statement of Reasons of June 13, 2003, except as noted immediately below.

The technical support document "No Significant Risk Levels (NSRLs) for the Proposition 65 Carcinogens Benzo[b]fluoranthene, Benzo[j]fluoranthene, Chrysene, Dibenzo[a,h]pyrene, Dibenzo[a,i]pyrene, and 5-Methylchyrsene by the Oral Route" included with this notice has been modified, based upon comments received, to delete a brief discussion comparing cancer potencies generated from intraperitoneal and oral route carcinogenicity studies of a related class of compounds called nitro-arenes. These

changes do not alter the NSRL values proposed for the six polycyclic aromatic hydrocarbons (PAHs) noted above that are the subject of the document.

In addition, language has been added to make clear that the methodology used in the above named document is equivalent to a potency equivalency factor approach. That is, the cancer potencies are scaled to that of a chemical with an adopted cancer potency, in this case, benzo[a]pyrene. A few editorial changes have also been made to the summary on the first two pages of the document. All changes are noted in underline/strikeout in Attachment 1.

The technical support document "No Significant Risk Levels (NSRLs) for the Proposition 65 Carcinogens Benz[a]anthracene (Oral) and 7H-Dibenzo[c,g]carbazole (Oral)" (Attachment 2) has been corrected on the eighth line of the paragraph on page 7 to read "upper confidence limits on q_1" instead of "upper confidence limits on q_1*." This change does not alter the NSRL values proposed in the document.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED

Three sets of comments were received regarding the NSRLs (oral exposures only) for the PAHs with one comment each from Misty L. Bogle of Reilly Industries, Inc., F. Jay Murray, Ph.D. of Murray and Associates on behalf of the American Coke and Coal Chemicals Institute, the Pavement Coating and Technology Center, and the Western States Petroleum Association, and Robert P. DeMott, Ph.D., of Exponent on behalf of the Pavement Coating and Technology Center.

Briefly, as discussed in detail in the initial statement of reasons, these PAH NSRLs are for oral exposures only, and were derived from long term cancer bioassay studies by the oral route (benz[a]anthracene and 7H-dibenzo[c,g]carbazole) and intraperitoneal route (benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, and 5-methylchrysene). Studies employing the intraperitoneal (i.p.) route (neonatal mouse model) were adjusted for by employing a correction, to take into account the relative differences in activities for i.p. versus oral exposure.

Benzo[a]pyrene was used as the reference compound for making the adjustment: The ratio in carcinogenic activity of the oral route to the i.p. route (neonatal mouse model) was the adjustment factor. The three commenters objected to this approach, and their objections are detailed below, along with OEHHA's responses to them. Two commenters (Ms. Bogle and Dr. Murray) asked that OEHHA utilize the potency equivalency factor approach utilized by OEHHA's air program, to establish inhalation cancer potencies for these PAHs (OEHHA, Air Toxics Hot Spots Program Risk Assessment Guidelines, Part II. Technical Support Document for Describing Available Cancer Potency Factors, December 2002). OEHHA notes that the approach used for oral NSRLs is equivalent to a potency equivalency factor approach, also using oral benzo[a]pyrene as the basis potency. The activities of chemicals relative to benzo[a]pyrene are judged by comparing their potency in i.p. studies to the potency of benzo[a]pyrene, also in the i.p. study. The OEHHA air program did use a similar

approach to establish inhalation potencies for PAHs; however, for this particular subset of chemicals, the studies utilized by the air program to establish relative differences in inhalation potencies were principally dermal studies (OEHHA, 2002). For the air program, the dermal route was judged to more closely approximate the inhalation route than either the oral or i.p. routes, as both inhalation and dermal absorption result in direct systemic distribution without initial distribution to the liver, a major site of metabolism and detoxification. In developing oral NSRLs; however, the i.p. route was judged to be preferable to the dermal route, as i.p. administration – like oral administration – results in systemic exposure with early distribution to the liver (Klaassen CD, 1986. Distribution, excretion, and absorption of toxicants. Klaassen CD, Amdur MO, Doull J, eds. *Casarett and Doull's Toxicology: The Basic Science of Poisons.* 3rd ed. Macmillan Publishing Co.: New York, p. 59). Moreover, internal dosing can be very precisely gauged using i.p. administration, reducing one area of uncertainty inherent in dermal application studies. In addition, tumors at multiple sites were evaluated in the i.p. studies under consideration here, whereas dermal studies generally examine only skin tumor development. Thus, the multi-site evaluation permitted by the i.p. study results assessed here was judged to provide a better means of assessing total relative cancer risks from oral exposures to these PAHs than would skin tumor data from the dermal studies of these PAHs.

Comment:
Misty L. Bogle commented that in establishing the NSRLs for the PAHs, OEHHA relied on data of questionable quality, citing a report from the U.S. Environmental Protection Agency (U.S. EPA) which noted the following overall shortcomings in the set of studies: non-typical routes of exposure, small study populations, single dose groups, and the failure to report dose-response data.

Response:
The study shortcomings noted by the commenter were taken into consideration and acknowledged by OEHHA in the draft document. While it is true that i.p. injection is not a likely route of human exposure, the difference between the i.p. and oral routes (the route for which NSRLs were developed) is explicitly taken into account. The i.p. studies employed a consistent methodological approach and design, adequate for making potency estimates relative to benzo[a]pyrene. For each of the six PAHs and benzo[a]pyrene, the i.p. studies employed a neonatal mouse model, with very similar dosing regimens. Multiple dose studies are preferable for making potency estimates; however, single dose studies are not unusual, and they can be reliably used to establish upper bound estimates of carcinogenic potency. The use of small numbers of animals in a given study does tend to increase uncertainty in the estimation of potency. This is taken into account statistically. In the studies utilized here, the significant tumor responses and numbers of animals with responses resulted in well-defined potency estimates for the studies, as reflected in the statistical confidence bounds associated with the potency estimates. The increase in tumors observed in a small group underscores the level of concern for a carcinogenic effect from exposure to these chemicals and provided the basis for the Proposition 65 listing of the chemicals. The regulation guiding the development of NSRLs provides that "the assessment shall be based on evidence and standards of comparable scientific basis to the evidence and standards which form the scientific basis

for listing the chemical as known to the state to cause cancer." (Title 22 Cal. Code of Regs. §12703(a)). OEHHA believes that the evidence and standards in the studies used in establishing the cancer potencies for these compounds are of comparable scientific basis to those which supported the original listing of the compounds. In the case of dibenzo[a,h]pyrene and dibenzo[a,i]pyrene, the studies used in establishing the NSRLs were among those supporting the listing of the chemicals as known to the state to cause cancer. Further, the studies used in establishing the cancer potencies were not used in isolation, but in conjunction with an oral study of the carcinogenicity of benzo[a]pyrene.

Comment:
The commenter, Misty L. Bogle, also noted the absence of a control group in the study supporting the NSRL for 7H-dibenzo[c,g]carbazole. This same comment was raised in the second set of comments from F. Jay Murray and is addressed in detail below in response to his comments.

Ms. Bogle also suggests that OEHHA's reference to similarities based on work done on nitropyrenes in support of the extrapolation may not be appropriate, due to possible differences in metabolism and mutagenic densities between nitropyrenes and PAHs lacking nitro groups. The commenter also stated that OEHHA's assertion that potencies generated from studies for this class of compounds by the i.p. route do not differ greatly from those by the oral route, "provided that other variables such as species and age at the time of exposure are similar" warrants further explanation.

Response:
OEHHA concurs that the information relating to the work done in estimating the cancer potencies of nitropyrene (nitro-arene) compounds has not been detailed to the point that it explains its relevance to the PAHs discussed in the draft document. The statements in the draft document relating to nitropyrenes (nitro-arenes) have been removed from the final document. The quoted statement has also been deleted from the document.

Comment:
Ms. Bogle noted that there is an inconsistency in approach within OEHHA itself and with U.S. EPA. - because the Air Toxics Program (in conjunction with the Air Resources Board) and the U.S. EPA, both use a "potency equivalency factor" (PEF) approach to assessing risks posed by PAHs relative to benzo[a]pyrene, a relatively well-studied compound.

Response:
As indicated above, the PEF approach in use by the U.S. EPA and the Air Toxics Hot Spots Program is conceptually equivalent to that used to derive NSRLs, except that skin painting promotion studies in mice for this subset of chemicals are used by U.S. EPA and the OEHHA Air Program to judge the differences in *inhalation* potencies relative to one another and i.p. studies are used by OEHHA to judge the differences in *oral* potencies relative to one another (for the development of the oral NSRLs). The oral NSRLs described here are applicable to oral exposure situations only. OEHHA has found that

oral cancer potencies are scientifically better supported by i.p. injection studies than by skin painting promotion studies.

Comment:
Jay F. Murray commented that the studies that formed the basis of the NSRLs are of insufficient quality and of unconventional design for quantitative risk assessment, with deficiencies including the lack of a control group, inadequate size, single dose groups, absence of statistical analysis, limited duration of exposure, limited reporting, and the absence of data on the purity of the test chemical. The commenter recommends an alternate approach, such as the potency equivalency factor (PEF) approach adopted under the Air Toxics Hot Spots Program and by the U.S. EPA. Further, the commenter points out that the regulations (Title 22 Cal. Code of Regs. §12703) require that the studies OEHHA uses must be "of sufficient quality" and "meet generally accepted scientific principles" and argues that the studies OEHHA selected do not meet these criteria. The commenter addresses the deficiencies in the approach to the quantitative risk assessment chemical-by-chemical, and OEHHA similarly responds chemical by chemical below. The commenter also states that none of the studies supporting the NSRLs has been used by a regulatory agency in establishing cancer potency factors for any of the eight PAHs.

Response:
OEHHA does not disagree with the commenter as to what aspects of study design are generally preferable for contributing to or for use in quantitative risk assessment. For example, a larger study with more animals and more dose groups is preferable to one with fewer animals and fewer dose groups. A main concern in study design is that the studies are too small to detect a carcinogenic response, and that the carcinogenic activity of the compound cannot be calibrated. However, the studies were of sufficient design to detect statistically significant increases in tumor incidence and to define carcinogenic activity for the potent PAHs in the studies discussed here. Regarding the point that statistical analysis was not presented in the studies, the relevant data are presented in the publication (in this case, the tumor incidence in the appropriate animal groups) and a risk analyst can perform statistical analyses. In this sense, the statistics reported by the authors are superfluous (although useful for some readers), while the raw data provided in the publications are essential. OEHHA performed the analyses during the course of assessing the study for quantitative risk assessment. With respect to the limited duration of exposure, the yearlong i.p. study for benzo[a]pyrene – which induced lung and liver tumors - was used to derive the i.p.-oral correction factor. The lengths of the i.p. studies relative to the study for benzo(a)pyrene is the critical consideration for addressing the importance of study duration. The i.p. studies for four of the six chemicals were of the same length (benzo[b]fluoranthene, benzo[j]fluoranthene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene). For two compounds (5-methylchyrsene and chrysene) the studies were of shorter duration (35 and 37-42 weeks, respectively), but not so much so that an inordinately large adjustment factor (< 3) was needed to normalize to the 52 week benzo[a]pyrene study. With regard to reporting on purity of test compound, Dr. Murray raised this issue for specific chemicals, and these are addressed in detail below. Overall, OEHHA disagrees that the studies used as the bases for assessing cancer risks for the PAHs were not "of sufficient quality" and did not "meet generally accepted scientific

principles." Title 22 Cal. Code of Regs §12703(a)(7) states that "[w]hen available data are of such quality that physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the risk assessment for inter-species, inter-dose, and inter-route extrapolations." OEHHA has determined that the available data concerning the relative cancer potency of benzo[a]pyrene by the i.p. and oral routes, the available i.p. bioassay data for six PAHs under consideration here, and the similar physicochemical properties among this class of chemicals (*i.e.*, PAHs) are sufficiently strong to use the data with confidence in establishing cancer potencies relative to benzo[a]pyrene.

Comment:
The commenter states that the 1963 Klein oral gavage study supporting the NSRL for benz[a]anthracene was conducted without a concurrent control group, the timing of dosing was not stated, the administered dose cannot be calculated because the body weights of the animals were not reported, the purity of the test chemical was not presented, there were only 20 animals in the treatment group, there was only one dose tested (which is not adequate to evaluate a dose-response), there was no statistical analysis, the pattern of dosing does not resemble human exposure (which is expected to be chronic and the animals in this study were administered two bolus doses near the time of birth), and the pattern of dosing for this chemical appears to make a substantial difference in estimates of cancer potency.

Response:
OEHHA recognizes that the vehicle control group (*i.e.*, the group receiving 0.1% methocel-Aerosol OT without benz[a]anthracene) in this study is an imperfect match to the treatment group selected for use in estimating the cancer potency; however, the degree of mismatch is relatively small – an optimally matched vehicle control group would have received two treatments with the vehicle alone, as compared to the 15 treatments with the vehicle alone received by the actual vehicle control group– and would not be expected to influence the development of tumors in the vehicle control group. The absence of a presentation of the body weights of the experimental animals is a relatively small omission, and introduces a small source of uncertainty for the estimation of dose applied to the animals. Mouse body weights can be readily estimated for neonatal or juvenile mice; in this case values were used based upon a database of age-dependent body weights of similar mice compiled by the U.S. EPA (U.S. EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Office of Health and Environmental Assessment, Washington, DC. EPA/600/6-87/008). Twenty animals per treatment group is an adequate number to establish statistically significant increases in tumor incidence and as a basis for a quantitative risk assessment. Examination of statistical confidence bounds shows that in this case the uncertainty resulting from sample size is small. In this case, statistically significant increases in liver and lung tumors were observed. While testing at multiple doses provides useful information about the shape of the dose-response curve, studies with single doses can be readily used to estimate upper-bound cancer potencies; again in this case the uncertainty associated with this procedure is small. Even though the studies' authors did not state the purity of the test substance, it is reasonable to assume that the chemical was supplied in a

form of adequate purity. In conducting carcinogenicity studies suitable for publication in the scientific literature, it is the practice of experimenters to use chemicals that are of appropriate grade, and it is the practice of the chemical industry to properly formulate, label and market its graded products. Without data supporting the claim that a low grade or contaminated product was used in a study (the commenter provided none), OEHHA assumes that product of suitable grade was used. The absence of statistical analysis by the authors presents no barrier to using this study in a quantitative risk assessment, as all the necessary information is presented in the data tables and results section, permitting independent statistical evaluation. Use of the Armitage-Doll dose weighting for the early-in-life exposure in this study takes into account the temporal pattern of dosing and provides a cancer potency estimate applicable to chronic exposure scenarios. The basis for the commenter's statement that the pattern of dosing for benz[a]anthracene appears to make a substantial difference in estimates of cancer potency was a direct and inappropriate comparison by the commenter of the potency estimates derived solely from dose-response data on hepatoma incidence that are presented in Table 5 of the document for Experiments I, IIa, and IIb. As noted in the text of the document and as footnote "a" of Table 5, the incidence of hepatomas in Experiment IIa was 100%, precluding calculation of q_1* (*i.e.*, the 95% upper confidence limits on q_1); thus the number presented in the table is the lower 95% confidence bound for the probability that all animals in the dosed group are tumor-bearing, and is not directly comparable to the 95% upper confidence limits on q_1 presented for experiments I or IIb. In addition, the commenter failed to take into consideration the induction of tumors at sites other than the liver by benz[a]anthracene (*i.e.*, lung: 37/39 in treated mice in Experiment I; 19/20 in treated mice in Experiment IIa; 17/20 in treated mice in Experiment IIb; forestomach: 2/39 in treated mice in Experiment I). As discussed in the NSRL document, OEHHA chose not to use the lung tumor data from these experiments in deriving human cancer potency estimates, due to the possible extreme sensitivity of the particular mouse strain employed (*i.e.*, B6AF$_1$/J) to developing lung tumors. A proper analysis of the effect that different patterns of dosing had on the estimated cancer potency of benz[a]anthracene in these experiments would necessarily be based on incidence data for all treatment-related tumors, however.

Comment:
Dr. Murray also states that 1) the 1950 Armstrong and Bonser oral gavage study supporting the NSRL for 7H-dibenzo[c,g]carbazole lacked a control group and is inappropriate for quantitative risk assessment. 2) Further, OEHHA's assumption that no tumors would have been observed in a hypothetical control group is inappropriate if based only on the authors' implication that forestomach tumors are uncommon in historical controls. 3) The group size of 30 mice is inadequate for a cancer bioassay, as was the number of dose groups (one). 4) The dose administered exceeded the maximum tolerated dose (MTD), with all mice showing signs of liver toxicity and mortality. 5) The excessive dosing violates a generally accepted scientific principle. 6) Dosing was also adjusted during the course of the study to permit survival, making interpretation difficult.

Response:
With regard to the first two points, OEHHA carefully considered the merits of using a study without a concurrent control group for the estimation of cancer potency. On balance, the study convincingly demonstrated a carcinogenic effect in several target organs, namely tumors of the forestomach, liver, bile duct, and lung. At a couple of sites, the tumor incidences were high (100% incidence of bile duct cystadenomas) or unusually severe (metastatic liver tumors), although the difficulty in estimating background incidence for all but the forestomach tumors precluded their use in quantitative risk assessment. The commenter suggests that OEHHA relied solely on the authors' implication that forestomach tumors are rare among these mice in order to justify making the assumption that no forestomach tumors would likely occur in a control group of mice. On the contrary, a large database of long-term studies in mice conducted by the National Toxicology Program (NTP Historical Control Information for the NIH-07 Diet, available at URL: http://ehis.niehs.nih.gov/ntp/docs/ntp_hcrs.html) and a review by the International Agency for Research on Cancer (IARC, 1994, Pathology of Tumours in Laboratory Animals. Volume 2. Tumours of the Mouse. Eds. V. Turusov and U. Mohr. IARC Scientific Publications, No. 111, Lyon, France.) also support this assumption and OEHHA felt it was reasonable to adopt this assumption for making a potency calculation for this clearly carcinogenic compound.

With regard to the point on study size, as stated above, a larger study with more animals and more dose groups is preferable to one with fewer animals and fewer dose groups. The 1950 Armstrong and Bonser study using 30 animals per group, and employing one dose level demonstrated a clear carcinogenic effect of 7H-dibenzo[c,g]carbazole at multiple tumor sites. This study is noted in a review of the carcinogenic effect of the compound and was used as evidence of its carcinogenicity in formal evaluations of the evidence for the compound (IARC, 1973. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 3. Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds, p. 265; NTP, 1985, Fourth Annual Report on Carcinogens). Since this source and study was considered as a basis for the listing of 7H-dibenzo[c,g]carbazole under Proposition 65, OEHHA considers it sufficient "evidence and standards of comparable scientific validity" (Title 22 Cal. Code of Regs. §12703(a)).

With regard to the fourth point, while toxicity during the course of an experiment can reduce survival, and mask the appearance of a carcinogenic effect, there was sufficient survival in the Armstrong and Bonser study to show a robust carcinogenic response at several sites. OEHHA does not agree that the dosing in the study violates a generally accepted scientific principle. In designing a cancer bioassay, it is desirable to minimize toxicity because reduced long-term survival makes it more difficult to discern a carcinogenic effect within a small group of animals. In this study, however, survival was adequate to manifest highly statistically significant increases in tumor incidence. The variable dosing during the course of the study did not undermine the finding that 7H-dibenzo[c,g]carbazole is a highly carcinogenic compound. The Armitage-Doll adjustment factor was applied to the calculated administered doses to account for this aspect of the study's design.

Comment:
Dr. Murray notes the studies supporting the NSRLs for benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, and 5-methylchrysene were similar in design, *i.e.*, i.p. injection studies in neonatal mice. The commenter expressed concerns that the test compounds were possibly inadvertently injected directly into the liver and this route of administration tends to bathe the liver in the compound. In addition, the commenter alleges that i.p. injection is dissimilar to likely routes of human exposure (ingestion and inhalation). The commenter further states that the compounds were also administered in a different temporal pattern from that expected for human exposure and this pattern would be expected to exaggerate the effect in mice.

Response:
OEHHA has no basis for believing that the investigators in the various i.p. injection studies injected the neonatal mice directly into the liver. The neonatal mouse model is an established protocol and it is implausible that the experiments were not performed appropriately. For this reason and since the commenter cited no specific source supporting this contention, OEHHA assumes that the studies were conducted appropriately. We agree that the i.p. route of exposure is dissimilar to likely routes of human exposure and that the pattern of exposure does not resemble human exposure (which is expected to be lifelong, rather than limited to the first 15 days of life). OEHHA, in deriving adult oral potencies for these six PAHs, divided the potencies calculated directly from studies by the i.p. route in the neonatal mouse model by a factor of 75, which is the ratio of the potency of benzo[a]pyrene derived from the neonate i.p. studies to the oral cancer potency (derived from oral studies in adult animals) used for regulatory purposes by U.S. EPA and OEHHA. The similarity of the i.p. studies in duration and pattern of dosing to the i.p. benzo[a]pyrene study results in a consistent and reliable adjustment for each of the PAHs.

Comment:
The commenter also suggests that OEHHA's use of a scaling factor to adjust cancer potencies derived from i.p. routes to those by the oral route is a "questionable practice" and not a generally accepted scientific principle. This approach was not used by OEHHA in its December 2002 Air Toxics Hot Spots Risk Assessment Guidelines (Part II. Technical Support Document for Describing Available Cancer Potency Factors). In establishing potencies in the OEHHA (2002) document, OEHHA did not use the studies supporting the NSRL, thus implying that OEHHA had found them inadequate for risk assessment, and OEHHA explicitly had reservations about the studies of benzo[a]pyrene, although these studies [according to the commenter] are more appropriate for risk assessment (multiple doses, longer exposure duration) than those for the other PAHs, for which the database was described as "relatively incomplete." The oral NSRLs for the PAHs based upon the approach are 1.1 to 20 times lower than the inhalation potencies presented in the Air Toxics Guidance for estimating cancer risks from inhalation exposures. The commenter contends that the NSRL approach is not scientifically more defensible than the PEF approach and that the U.S. EPA has not been inclined to conduct a quantitative risk assessment based upon the same studies used by OEHHA. The commenter states that the U.S. EPA is expected to complete an assessment of PAH

mixtures in 2005. Finally the commenter contends that the absence of risk assessments by other regulatory agencies of the eight PAHs under consideration here suggests that the studies are not scientifically suitable for quantitative risk assessment.

Response:
As discussed above, in principle, the approach to the extrapolation of cancer potencies from i.p. injection studies is equivalent to the PEF approach used in the Air Toxics Hot Spots document, except that skin painting studies are used in the Hot Spots document for this subset of chemicals to estimate inhalation potency and i.p. studies are used in the NSRL document to estimate oral potencies. In the derivation of PEFs in the Hot Spots document, cancer potencies from skin painting studies in mice were scaled relative to skin painting studies conducted with benzo[a]pyrene, the relative potency of each compound is then applied to the cancer potency of benzo[a]pyrene by the oral route. One difference is that the scaling factors (PEFs) in the Hot Spots document are essentially rounded to an order of magnitude, whereas in the proposed NSRL document, the calculated scaling factor was applied directly to the derived i.p. injection potency values for each compound. Cancer potencies derived from carcinogenicity studies by the oral route are most suitable for the estimation of cancer potency by the oral route. In the absence of appropriate studies by the oral route, a PEF approach utilizing carcinogenicity studies by the i.p. route is more suitable than one relying on skin painting studies when estimating cancer potency by the oral route for the following reasons: (1) i.p. administration, like oral administration, results in systemic distribution of the chemical including early distribution to the liver (Klaassen CD, 1986. Distribution, excretion, and absorption of toxicants. Klaassen CD, Amdur MO, Doull J, eds. *Casarett and Doull's Toxicology: The Basic Science of Poisons.* 3rd ed. Macmillan Publishing Co.: New York, p. 59) whereas dermal application, like inhalation exposure tends to initially bypass distribution to the liver; (2) internal dosing can be very precisely gauged using i.p. administration, reducing one area of uncertainty inherent in dermal application studies. The potencies derived in the NSRL document are limited to oral route exposures only.

Comment:
Robert P. DeMott commented that Exponent believes the fundamental limitations of the available studies and approaches do not meet the requirements specified in Title 22 Cal. Code of Regs. §12703. "The proposed NSRLs should be reconsidered and revised" because the studies do not meet necessary criteria and injection studies in mice are not appropriate for extrapolation to long-term human ingestion. Further comments were made on a chemical-by-chemical basis.

The commenter states the potency estimate for benz[a]anthracene is based on a study with a small group of animals dosed only twice (Klein, 1963). U.S. EPA considered this study inappropriate for quantitative risk assessment because of the study design, though the Agency did consider it in establishing the weight of evidence for carcinogenicity. The commenter alleges that the study does not meet the principles and requirements of Title 22 Cal. Code of Regs. §12703. More than one dose level is necessary to characterize the dose-response characteristics. The potency estimates from the two studies of animals dosed 15 times over five weeks were consistent with each other, but

inconsistent with (and lower than) those dosed only two times, indicating the protocols were not comparable. U.S. EPA recommends using results from more than one sex and species in deriving cancer potencies. The benz[a]anthracene treatment in the Klein study was likely acutely toxic and irritating and is reasonably expected to result in a tissue-damage related tumor response. OEHHA's approach to interspecies scaling (one-third power) is outdated and should be updated.

Response:
OEHHA disagrees with these comments. The studies relied on by OEHHA are adequately conducted and reported for risk assessment purposes. The appearance of statistically significant increases in tumor incidence from two exposures to a chemical raises concerns about the carcinogenicity of such a compound. OEHHA's selection of the cancer potency from the most sensitive study is consistent with Title 22 Cal. Code of Regs. §12703(a)(4) ("Risk analysis shall be based on the most sensitive study deemed to be of sufficient quality."). As stated earlier, testing at multiple doses provides useful information about the shape of the dose-response curve, but studies conducted with single doses can be readily used to estimate upper-bound cancer potencies. As discussed above and in the NSRL document, OEHHA chose not to use the lung tumor data from these experiments in deriving human cancer potency estimates, due to the possible extreme sensitivity of the particular mouse strain employed to developing lung tumors. As also discussed above, the conclusions drawn by the commenter, based upon direct comparison of the animal cancer potency estimates derived solely from hepatoma incidence data for the different protocols are not appropriate. Briefly, for one study the 95% upper confidence limit on q_1 could not be calculated, due to 100% incidence of hepatomas in the treated group. OEHHA instead presented the lower 95% confidence bound for the probability that all animals in the dosed group were tumor-bearing; this value is not directly comparable to the 95% upper confidence limits on q_1 presented for the two other protocols. Furthermore, a proper comparison of the estimates of cancer potency of benz[a]anthracene in these studies would require analysis of all treatment-related tumors, including lung adenomas. The compounds studied no doubt were toxic to the animals, but there is not a clear basis for believing that these clearly genotoxic compounds induce tumors by a mechanism that is strictly based on their ability to cause tissue damage. For this reason, OEHHA has chosen to use a low-dose linear approach in the quantitative risk assessment. OEHHA's approach to interspecies scaling is based on Title 22 Cal. Code of Regs. §12703(a)(6) which provides that "Interspecies conversion of animal cancer potency to human cancer potency shall be determined by multiplying by a surface area scaling factor equivalent to the ratio of human to animal bodyweight, taken to the one-third power."

Comment:
The commenter states the cancer potency for 7H-dibenzo[c,g]carbazole is highly uncertain because of the high doses which resulted in toxicity and death in most of the treated animals in the selected study (Armstrong and Bonser, 1953), making the study unsuitable for cancer potency derivation. Further, the study did not have a control group and OEHHA's assumption that no forestomach tumors would have been observed is a highly uncertain approach. Tumors that result from point-of-contact – in this case

forestomach tumors – are not typically used for quantitative risk assessment. Humans also do not have forestomachs, further limiting interpretation of the results of the study.

Response:
The Armstrong and Bonser study produced tumors to an unusual degree despite some degree of toxicity to the exposed animals, and OEHHA considers the incidence of tumors among the survivors (or those that died with tumors) suitable for risk assessment purposes. As stated earlier, the absence of a control group in the studies was outweighed by the convincing demonstration of a carcinogenic effect. The selection of the forestomach tumors as the basis for the potency derivation has considerable certainty compared to that of the other sites for which tumors were observed (liver, lung, bile duct), since tumors at this site appear very rarely in untreated animals. With respect to the absence of a forestomach in humans, the interpretation of the cancer potency is more one of concern for cancer causing potential to a given individual or organism, rather than an extension of an observation to a specific organ or tissue, so strict site-concordance for tumor sites is not expected.

Comment:
The commenter states that the cancer potencies for benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene and 5-methylchrysene were derived from multiple studies using different strains of mice and different durations between dosing and evaluation of tumor incidence. The use of benzo[a]pyrene as an internal standard for potency comparison is an unusual and unprecedented approach, and therefore inconsistent with the requirements and principles of Section 12703. U.S. EPA recommends against using route-to-route extrapolation completely. The i.p. and oral routes of exposure to benzo[a]pyrene produce different tumors indicating differences in mechanisms of toxicity, absorption, distribution and metabolism between the routes, which even OEHHA acknowledges confounds the results of the studies. It is uncertain as to whether the relationship between the potency for the two routes of exposure for benzo[a]pyrene will hold for other polycyclic aromatic hydrocarbons, and using a similar argument based upon the potencies of a different class of compounds (nitro-arenes) is not an adequate assumption for a different group of chemicals.

Response:
The variability of dosing and duration are readily adjusted for using the Armitage-Doll correction factor. While this adjustment factor requires an assumption about the relationship between age of exposure and cancer risk (risk rising proportionally to the third power of age), this adjustment is not unconventional and provides a reasonable basis for normalizing dosing between studies. The use of an internal standard for scaling cancer potencies of related compounds, while relatively unusual in the universe of quantitative risk assessments for carcinogens, is not unprecedented. Scaling factors have been applied in the potency equivalence factor (PEF) scheme for polycyclic aromatic hydrocarbons in the past, and toxicity equivalence factors (TEFs) have been applied to compounds related to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), in both cases equivalence factors are derived from experimental data from studies aimed at assessing

the relative activity of these compounds pertinent to carcinogenicity (OEHHA, 2003. Technical Support Document for Describing Available Cancer Potency Factors. Appendix A. Use of the Revised Toxicity Equivalency Factor (TEF_{WHO-97}) Scheme for Estimating Toxicity of Mixtures of Dioxin-Like Chemicals; Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M *et al*., 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ Health Perspect* 106(12):775-92; Van den Berg M, Peterson RE, and Schrenk D, 2000. Human risk assessment and TEFs. *Food Addit Contam* 17:347-58). OEHHA recognizes some of the uncertainty in applying a scaling factor to estimate the cancer potencies of a group of chemicals, namely in the implicit assumption that the pharmacokinetic aspects of behavior of each of the compounds at issue here are similar. However, in the case of these PAHs, there is a strong and consistent experimental basis for estimating relative potencies, which, in the absence of more suitable data, provides a reasonable basis for estimating cancer potency by the oral route. For these reasons, OEHHA believes that more appropriate scientific assumptions and principles are not available, consistent with Title 22 Cal. Code of Regs §12703(a). OEHHA agrees that the statements regarding the similarity of these PAHs to nitro-arenes compounds have not been discussed to the degree necessary to support them, and has removed from the NSRL document that element of support for the proposed NRSLs for PAHs.

Comment:
The commenter states that the protocols for exposure of the i.p. exposures is considerably different from that for the oral potency estimate for benzo[a]pyrene. In particular, the comment states the oral benzo[a]pyrene potency used by OEHHA as the basis for comparison is not the one proposed by U.S. EPA. OEHHA selects the high end of a range of potencies (11.7 $(mg/kg\text{-}day)^{-1}$), whereas U.S. EPA selects the mean (7.3 $(mg/kg\text{-}day)^{-1}$), thus U.S. EPA makes use of more of the available data. In spite of OEHHA's precedent in not choosing a mean for the oral cancer potency for benzo[a]pyrene, OEHHA chose a mean for the i.p. potency of chrysene in this NSRL document.

Response:
As the basis for the extrapolation, OEHHA used the cancer potency for benzo[a]pyrene of 11.7 $(mg/kg\text{-}day)^{-1}$ which serves as the basis of the NSRL for that compound (Title 22 Cal. Code of Regs. §12705) and for other OEHHA programs. A consistent approach was used in calibrating the carcinogenic potency of the i.p. studies for benzo(a)pyrene and the six other PAHs and the designs of the studies were similar. This contributes to the reliability of the potency estimates for these compounds. In the case of the cancer potencies for chrysene, there was not a clear basis for selecting one study over another, so the mean was chosen. It should also be noted that the potencies for the two chrysene studies that formed the basis for the mean were very close to each other, 140 and 160 $(mg/kg\text{-}day)^{-1}$.

Comment:
The commenter states that potency estimates were converted to human equivalents prior to deriving the route-to-route adjustment factor. Since the calculation of human equivalents is an exponential function – a function of body weights that may differ

between studies – it would make a difference in the scaling if the adjustment factors were applied before establishing the route-to-route extrapolation.

Response:
OEHHA determined that it was more appropriate to calculate the cancer potencies on an equal body weight basis before estimating and applying the route-to-route scaling factor. The cancer potencies for the animals are more appropriately compared to each other following bodyweight scaling to a single standard body weight. In this case, the human body weight was deemed appropriate since, ultimately, human cancer potencies were of interest. Practically, there is very little difference between the approaches identified by the commenter, since all the studies at issue here were conducted in mice and uniform assumptions about mouse body weights were made.

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.5(a)(7), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed, or would be as effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective and less burdensome to affected persons, than the proposed regulation.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses “no significant risk” of cancer (Health and Safety Code section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to provide “safe harbor” levels for certain chemical exposures. In other words, this regulation establishes the numerical no significant risk levels for eight carcinogens. At or below these levels, the Act does not require a warning regarding cancer or prohibit discharges to sources of drinking water based on carcinogenicity concerns. Thus, these levels will allow persons subject to the Act to determine whether a given discharge to sources of drinking water or exposure to people involving these chemicals is subject to the warning requirement and discharge prohibition provisions of the Act related to the risk of cancer or occurrence of reproductive toxicity (Health and Safety Code sections 25249.6 and 25249.5, respectively).

Although Title 22 Cal. Code of Regs. §12803 describes principles and assumptions for conducting risk assessments to derive safe harbor levels, many businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees needs the ability to determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Given the wide use of several of the chemicals covered by this regulation, the absence of this regulation

would leave numerous businesses without an efficient way of determining if they are in compliance with the Act without the expenditure of significant resources on their part.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. It should be noted that Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.